HIV-Negative Brother and Sister with Decreased CD4/CD8 Ratios and Different-Type Nephritides

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Dear Sir,

We describe here 2 HIV-negative siblings with decreased CD4/CD8 ratios and renal disease. The parents were unrelated. The brother, at age 1 year and 9 months, suffered from transient agranulocytosis. Serum IgG, IgA, and IgM were elevated at 1,270, 156, and 127 mg/dl, respectively. At age 1 year and 11 months, a microscopic hematuria was noted at which time serum IgG and IgA were still elevated, while serum IgM was 31 mg/dl. At age 4, streptococcal pharyngitis temporarily worsened the urinary finding. One month later, we noticed petechiae on his abdomen. The diagnosis of idiopathic thrombocytopenic purpura was made. Coin-cidentally, he showed a selective IgM deficiency. Serum complements were normal. No autoantibodies to nuclei, lymphocytes or DNA were detectable. Serum immune complexes were detected transiently. Thrombo-cytopenia was improved with oral prednisolone and serum IgM rose to 40 mg/dl. He normally had IgM isohemagglutinin to B group substances. Renal biopsy performed when he was on 20 mg/day prednisolone, revealed stage I membranous nephropathy with granular deposition of IgG (2+), IgA (1+), C1q (3+), C3 (2+), and C4 (1+) along the glomerular basement membrane, but not IgM. The microscopic hematuria continued even after the disappearance of proteinuria. Lymphocyte subsets are shown in table 1. B-cell subpopulations were within the normal or nearly normal range. Lymphocytes were poorly transformed by either PHA or Con A, and the activity of ADCC was decreased, despite being on 30 mg/day prednisolone. He had no antibody to either HIV-1 or HTLV-1.

At age 4 years and 6 months, whilst on 15 mg prednisolone every other day, he developed fever and swelling of the axillar lymph nodes. Neither cervical nor inguinal lymph nodes were involved. He showed pan-cytopenia and hypercellular bone marrow (M/E ratio, 6.24). Serum IgM was 15 mg/dl, but IgG and IgA were still elevated. Serum β 2-microglobulin was increased at 3,950 ng/ml. Antilymphocyte antibody was detected transiently.

During the subsequent 3-year follow-up, leukocytopenia, anemia, and thrombocytopenia developed either simultaneously or not simultaneously, and mild-to-serious bacterial infections also occurred. Axillar lymph node swelling waxed and waned. These hematologic abnormalities and the axillar lymph node swelling appeared to correlate with each other, and were responsive to an increased dosage of prednisolone. At age 7 years and 8 months, he died of intracranial bleeding due to thrombocytopenia while he was suffering from pneumonia.

Table 1. Lymphocyte subsets

As for the sister, a transient macroscopic hematuria was noticed at age 8 when she suffered an upper respiratory tract infection. Axillar lymph nodes were swollen, but the other superficial lymph nodes were not involved. Laboratory examination revealed: serum IgG, 1,570 mg/dl; IgA, 400 mg/dl; IgM, 162 mg/dl; serum complements, normal; serum β 2-microglobulin, 3,870 ng/ml; and autoantibodies, undetected. Lymphocyte subsets are shown in table 1. CD4⁺ CD8⁺ double-negative lymphocyte (CD3⁺ CD4⁺ CD8⁺) count was 5%.

Renal biopsy revealed mesangial proliferative glomerulonephritis with focal mononuclear cell infiltration into the interstitium, lymph follicle formation, and focal tubular atrophy.

Mesangial deposition was shown of IgA (2+) and C1q (2+). IgG, IgM, C3, and properdin were stained faintly ($\pm$ to 1+). A combination of prednisolone, dipyridamole, and aspirin was administered orally. Soon the proteinuria disappeared, but the microscopic hematuria continued. The axillar lymph

nodes became nonpalpable. No antibody to either HIV-1 or HTLV-1 was detected. She had chronic tonsillitis and almost always showed postnasal discharge during the 2.5-year follow-up. Nine months after the cessation of steroid therapy, the axillary lymph node on the left side was enlarged again. Subsequently, the bilateral lymph nodes waxed and waned without complete involution. She has not developed anemia, thrombocytopenia, or leukocytopenia. The apparently healthy mother had a past history of tonsillectomy for chronic tonsillitis. At age 33, chest X-ray showed an abnormal shadow in the left lung apex lasting 3 years. Urinary abnormalities have not been pointed out. Lymphocyte subsets at age 38 are shown in table 1.

Serum IgG level was

1,530 mg/dl, IgA 616 mg/dl, IgM 450 mg/dl, IgD 5 mg/dl, and IgE 8 U. Thus, she had abnormalities similar to those in the daughter. In the apparently healthy, then 41-year-old father, the serum IgG level was 2,100 mg/dl, IgA 260 mg/dl, IgM 98 mg/dl, IgD 7 mg/dl, and IgE 59 U. Lymphocyte subsets are shown in table 1. CD4⁺ CD8⁺ double-positive (CD4⁺ + CD8⁺ CD3⁺) lymphocyte count was 10%. None of the subjects had a past history of blood transfusion.

Although the characterization of immunologic abnormalities in this family remains insufficient, these abnormalities are thought to be responsible for the nephritides in the siblings in the same way as in AIDS patients with decreased CD4/CD8 ratios [1-3].

References

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